Journal of Surgical Oncology 1998;69:66–70

Liver Resection of Noncolorectal Secondaries

GERT LINDELL, MD, PhD,* BJÖRN OHLSSON, MD, ARTO SAARELA, MD, ROLAND ANDERSSON, MD, PhD, AND KARL-GÖRAN TRANBERG, MD, PhD
Department of Surgery, Lund University, Lund, Sweden

Background and Objectives: Hepatic resection of noncolorectal metastases appears to be performed with increasing frequency. Reported experience is limited and indications are controversial.
Methods: Retrospective review of curative hepatic resection in 32 patients (median age 58 years) during 1970–1995. The primary tumor was a carcinoid in seven patients, other endocrine tumor in five patients, malignant melanoma in three patients, stomach cancer in three patients, exocrine pancreatic cancer in two patients, gynecological cancer in two patients, sarcoma in two patients, and miscellaneous in eight patients. Seven patients (22%) had bilobar disease and 12 patients (38%) had extrahepatic growth.
Results: Median survival was 32 months, and 5-year actuarial survival rate was 36% (including operative mortality). Median survival in the endocrine (n = 12) and nonendocrine (n = 20) groups was 72 and 18 months, respectively (corresponding 5-year survival rates were 56 and 25%) ($P = 0.16$). Prognostic factors could not be established in either group. It is, however, noteworthy that no patient with nonendocrine secondaries and more than one liver tumor or extrahepatic disease survived for 5 years. Major complications were seen in eight patients (25%), including three postoperative deaths (operative mortality 9%) occurring during the first 5 years of the study period.
Conclusions: Hepatic resection of metastases from endocrine primary tumors was followed by long-term survival in a substantial proportion of patients. Long-term survival for patients with nonendocrine tumors was observed only when there was a single liver tumor and no extrahepatic growth. Further experience is needed for definition of resection criteria.
J. Surg. Oncol. 1998;69:66–70.

KEY WORDS: **hepatic resection; liver metastases; noncolorectal; endocrine**

INTRODUCTION

Hepatic resection has gained acceptance as a potentially curative treatment for primary liver cancer or secondaries originating from the colon or rectum. However, its role in metastatic disease from other malignancies is controversial. Several authors suggest that liver resection of noncolorectal secondaries, unless from Wilms tumor, should be discouraged [1–4], whereas others take the view that selected patients are candidates for hepatic resection [5–8]. The aim of this study was to review our experience of liver resection of noncolorectal secondaries in an attempt to find determinants of success and failure.

MATERIALS AND METHODS

Patients

The charts of all patients undergoing curative resection for noncolorectal liver secondaries during 1970–1995 were reviewed. Resection was defined as curative when it was considered intraoperatively that all tumor was removed. There were 18 women and 14 men, with a median age of 58 (range 32–77) years. Six patients were alive at the time of review (June 1, 1997), and median

*Correspondence to: Gert Lindell, MD, Department of Surgery, Lund University, S221 85 Lund, Sweden. Fax No.: (46)46-172-335.
E-mail: gert.lindell@helsingborg.mail.telia.com
Accepted 28 May 1998

TABLE I. Noncolorectal Liver Metastases: Patient Characteristics

Variable	Endocrine (n = 12) No. (%)	Nonendocrine (n = 20) No. (%)	All (n = 32) No. (%)
Symptoms of liver tumor			
No	5 (42)	13 (65)	18 (56)
Yes	7 (58)	7 (35)	14 (44)
Time of diagnosis			
Synchronous	8 (67)	8 (40)	16 (50)
Metachronous	4 (33)	12 (60)	16 (50)
Time from diagnosis to resection			
<3 months	9 (75)	19 (95)	28 (88)
≥3 months	3 (25)	1 (5)	4 (12)
Tumor number			
<4	9 (75)	19 (95)	28 (88)
≥4	3 (25)	1 (5)	4 (12)
Tumor replacement of liver volume			
<25%	8 (67)	14 (70)	22 (69)
25–50%	2 (17)	6 (30)	8 (25)
50–75%	2 (17)	0 (0)	2 (6)
Tumor distribution			
Unilateral	10 (83)	15 (75)	25 (78)
Bilateral	2 (17)	5 (25)	7 (22)
Vascular invasion			
No	9 (75)	19 (95)	28 (88)
Yes	3 (25)	1 (5)	4 (12)
Overgrowth to other organs			
No	11 (92)	17 (85)	28 (88)
Yes	1 (8)	3 (15)	4 (12)
Extrahepatic metastases[a]			
No	7 (58)	13 (65)	20 (62)
Yes	5 (42)	7 (35)	12 (38)
Resection margin			
0 mm	3 (25)	5 (25)	8 (25)
1–10 mm	4 (33)	6 (30)	10 (31)
>10 mm	5 (42)	9 (45)	14 (44)
Type of liver resection			
Anatomical	9 (75)	12 (60)	21 (66)
Atypical major	1 (8)	3 (15)	4 (12)
Atypical minor	2 (17)	5 (25)	7 (22)
Intraoperative blood transfusion, units, median (range)	5 (0–23)	7 (0–15)	6 (0–23)

[a]Metastases to liver hilum lymph nodes was observed in three patients and was always associated with extrahepatic disease at other sites.

follow-up time for these patients was 11 (range 4–23) years. No patient was lost to follow-up.

Table I summarizes patient characteristics. The sites of the primary tumors are given in Table II. About one-third (n = 12) of the patients had endocrine tumors, the most common tumor being a carcinoid with the primary lesion in the small intestine (n = 6) or colon (n = 1). In the nonendocrine series, both gastric carcinoma and malignant melanoma contributed, with 3 patients. Single patients had cancers originating in the esophagus, duodenum, anus, kidney, breast, lungs, maxilla, or pineal gland (pineoblastoma).

Symptoms such as local discomfort/pain, diarrhea, and vasomotor disturbances were present in 9/20 (45%) patients with endocrine disease. Six of 20 (30%) patients with nonendocrine tumor had local discomfort or pain. Two patients in the endocrine group had ascites. Weight loss exceeding 3 kg was observed in 9 patients of 32 (28%).

Operative Procedures and Additional Treatment

Twenty-one patients underwent formal anatomical resections, and 11 patients had atypical resections. The primary tumor and the liver metastases were resected synchronously in 14 patients; operations for the primary tumor ranged from local excision to a Whipple procedure. Two patients underwent intestinal resection simultaneously with right or left hepatectomy; one patient had a carcinoid tumor in the small intestine with multiple metastases in the right liver lobe, and the other patient had a small intestinal carcinoma with two metastases in the left lobe. Dissection of the hepatoduodenal ligament revealed lymph node metastases in three patients.

Hepatic reresection was carried out 9 months after the first liver resection in a patient with endocrine pancreatic cancer. Postoperative adjuvant treatment with cytotoxic drugs was given to three patients with breast cancer, malignant melanoma, or carcinoid. One patient was treated with arterial embolization for hepatic recurrence of carcinoid tumors, and one patient was treated with dearterialization and chemotherapy due to hepatic metastases from soft tissue sarcoma. Another five patients were treated with cytostatic drugs for hepatic or extrahepatic recurrence (endocrine tumors two, malignant melanoma one, pineoblastoma one). The drugs and route of administration varied.

Evaluation

Survival times are actuarial and were calculated with the Kaplan-Meier method. Differences in survival times were estimated with the log-rank test. A two-tailed P value of < 0.05 was regarded as significant. Operative mortality was included in the survival figures (except in the analysis of prognostic determinants) and was defined as death within 30 days following surgery or before discharge from hospital. The endpoint for survival was death, irrespective of cause.

RESULTS

Survival times are shown in Table II. Median survival in the whole series was 32 months, with 1- and 5-year survival rates of 75 and 36%, respectively. Eight patients (25%) lived for more than 10 years after liver resection. Six of the long-term survivors are alive without evidence of recurrence, whereas two died of recurrent disease 15 years after liver resection. Median survival in the endocrine group (n = 12) was 72 months, and the 5-year survival rate was 56%. Median survival in the nonendo-

TABLE II. Survival and Recurrence Pattern After Liver Resection of Noncolorectal Liver Metastases

Primary tumor (no.)	Survival in all patients (months)	Survival in patients with extrahepatic disease (months)	NED[a]	Hepatic recurrence[b]	Extrahepatic recurrence only
Endocrine					
Carcinoid (7)	19, 38, 72, 138,[c] 140,[c] 177, 282[c]	38, 72, 177, 282	3	4 (3)	
Endocrine pancreas (2)	0.1, 99	0.1		1 (1)	
Adrenal gland (2)	10, 50			2 (2)	
Thyroid gland	55[c]		1		
Nonendocrine					
Stomach (3)	5, 14, 138[c]	14	1	2 (2)	
Malignant melanoma (3)[d]	5, 51, 184			1	2
Exocrine pancreas (2)	0.8, 5	0.8, 5			1
Sarcoma (2)[e]	26, 309	26	1	1	
Esophagus	19			1	
Duodenum	0.9				
Anus	14	14			1
Kidney	17	17		1 (1)	
Breast	81				1
Ovary	40				1
Uterus	27			1 (1)	
Lung (bronchial carcinoma)	185[c]		1		
Maxilla	10	10			1
Pineoblastoma	15			1	

[a]NED, no evidence of disease.
[b]Figures within parentheses denote patients with hepatic recurrence only
[c]Still alive.
[d]Two cutaneous and one ocular (long-term survivor).
[e]Retroperitoneal and gastric (long-term survivor; both were poorly differentiated).

crine group (n = 20) was only 18 months, but the 5-year survival rate was 25%, and 4/20 (20%) patients lived for more than 10 years after hepatic resection (Fig. 1). There was a substantial relief of systemic tumor effects in patients with carcinoid disease.

Twenty-two patients died from recurrent disease, which was located in the liver in 15/29 (52%, operative mortality excluded) and at extrahepatic sites in 12/29 (41%) patients. Relapse in the liver alone was observed in 10/29 (34%) patients.

Time to recurrence was similar in patients with endocrine and nonendocrine tumors (median values of 14 and 10 months, respectively), whereas survival after recurrence was longer in the endocrine group (median 36 months) than in the nonendocrine group (median 3 months).

None of the common prognostic determinants had a demonstrable influence on survival (Table III). Patients with extrahepatic metastases tended to have a worse prognosis than patients without, but the difference was not significant ($P = 0.23$). Bilateral disease, number of liver metastases, resection margin, or liver tissue replaced by tumor did not seem to vary with survival.

Long-term survivors had both synchronous and metachronous disease and no consistent pattern of liver tumor volume or blood transfusion. In the endocrine group, the four patients surviving for more than 10 years had one or two liver tumors in one lobe of the liver, two had extrahepatic disease, and two had a resection margin <10 mm. Another two patients survived for more than 5 years; both had multiple liver tumors and one each had bilateral disease, extrahepatic tumor, and a resection margin <10 mm. In the nonendocrine group, no patient surviving for more than 5 years (n = 5) had more than one liver tumor or extrahepatic disease, and one had bilateral disease. One of five 10-year survivors and two 5-year survivors had a resection margin <10 mm.

Three patients from a group of 32 (9%) died postoperatively because of intraabdominal abscess formation (n = 2) or liver necrosis (n = 1) and were operated on during the first 5 years of the study period. In two of them subtotal pancreatectomy was performed simultaneously with liver resection (one major and one minor atypical resection); in the third patient small bowel resection was performed together with a liver monosegmentectomy. Major complications occurred in another 5/32 patients (16%) (Table IV). Postoperative hospital stay was 12 (range 6–191) days.

DISCUSSION

The outcome of this retrospective study indicates that liver resection benefited some of the patients with noncolorectal liver secondaries. Hepatic resection gave long-term survival and substantial relief of symptoms in pa-

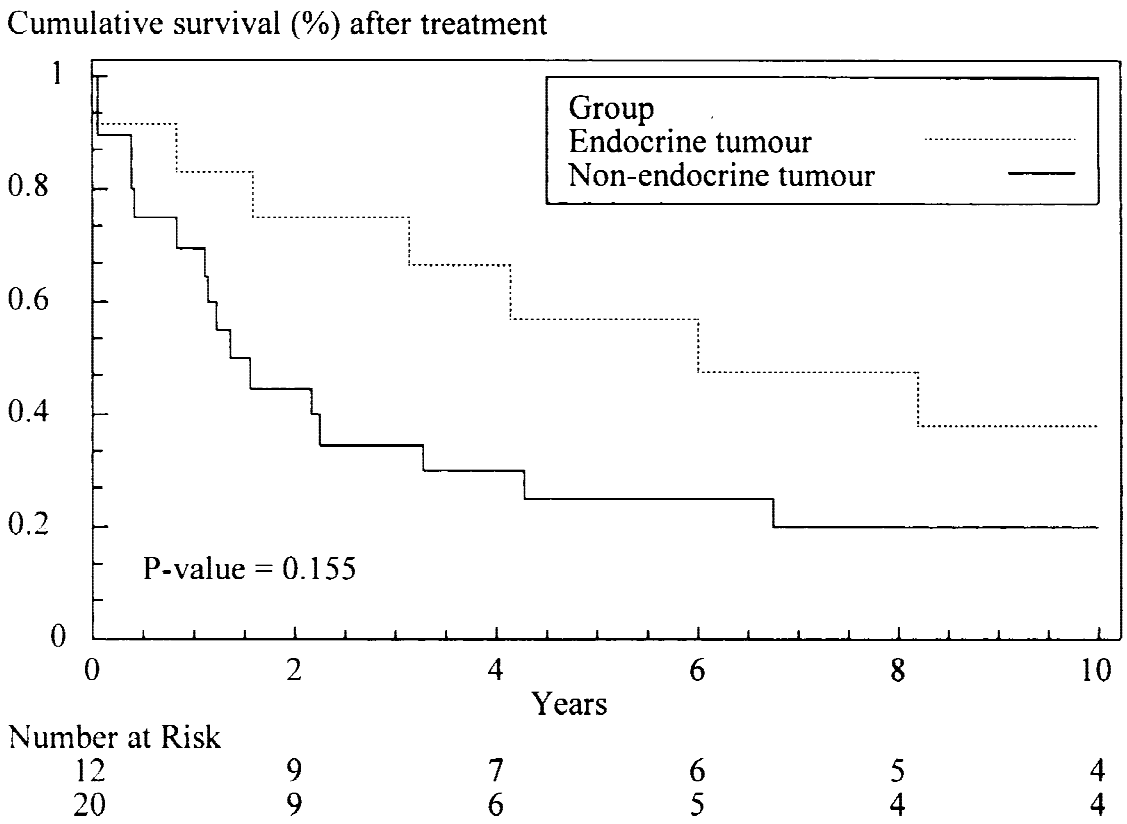

Fig. 1. Resection of noncolorectal liver metastases. Actuarial survivals in the endocrine and nonendocrine groups.

tients with endocrine secondaries, especially those from carcinoids. In addition, our experience suggests that hepatic resection may give long-term survival and occasional cure also for patients with noncolorectal, nonendocrine secondaries. The median survival in the nonendocrine group was only 18 months, but the 5-year survival rate was 25%, and 4 out of 20 patients lived for more than 10 years after hepatic resection. The latter figures are comparable with those observed after hepatic resection of colorectal metastases [9,10].

Although metastases to the liver indicate generalized disease in most patients, the incidence of isolated hepatic metastases from cancers of the colon or rectum is frequent enough to justify hepatic resection in selected patients [9,10]. The incidence of isolated hepatic metastases is substantially lower in noncolorectal malignancy [11], which explains why hepatic resection for noncolorectal secondaries has received limited attention and why some authors have concluded that hepatic resection should not be performed when the primary is of noncolorectal origin [1–4]. It appears, however, that the suggestion that noncolorectal liver secondaries should not be resected is too pessimistic. Several groups have reported that there was no difference in survival rate between patients resected for colorectal liver metastases and patients undergoing liver resection for noncolorectal metastases [5–8]. Long-term palliation, and probably improved survival, has been reported following hepatic resection of metastases from Wilms tumor, hypernephroma, and neuroendocrine tumors [1–8,12–19]. In a recent review on hepatic resection of noncolorectal, nonendocrine tumors, Schwartz [20] concluded that the prognosis was distinctly poorer than in patients having liver resection for colorectal metastases but that resection should be performed for liver metastases from hypernephroma or Wilms tumor and perhaps for adrenocortical carcinoma. Hepatic resection of other noncolorectal, nonendocrine tumors has only rarely resulted in long-term survival [1–8,12–20], although a few recent reports have suggested that rare patients with hepatic metastases from soft tissue sarcoma [21,22], melanoma [23] or metachronously from gastric carcinoma [24] may benefit from resection.

Criteria for resection of noncolorectal hepatic secondaries are presently difficult to establish. Our study did not show any clear-cut prognostic factor for endocrine metastases. As for nonendocrine metastases, no patient with more than one liver tumor or extrahepatic disease was a long-term survivor. Our attempt to identify other prognostic factors was not successful, but it should be emphasized that type II errors are likely due to the small number of patients. Further studies are needed to elucidate differences, if any, in prognosis for different primary

TABLE III. Resection of Noncolorectal Liver Metastases: Prognostic Determinants (n = 29)*

Variable	No.	Median survival (months)	5-year survival (%)	Log-rank *P* value
Time of diagnosis				
Synchronous	14	50	47	0.43
Metachronous	15	33	35	
Tumor number				
<4	25	40	39	0.48
≥4	4	55	50	
Tumor replacement of liver volume				
≤25%	19	26	37	0.44
>25%	10	51	48	
Tumor distribution				
Unilateral	23	50	43	0.60
Bilateral	6	27	25	
Overgrowth to other organs				
No	25	50	42	0.68
Yes	4	28	25	
Extrahepatic metastases				
No	19	51	46	0.23
Yes	10	21	30	
Resection margin				
≤10 mm	16	23	47	0.59
>10 mm	13	50	46	
Peroperative blood transfusion				
≤4 units	11	27	34	0.55
>4 units	18	50	40	

*Operative mortality (n = 3) excluded.

TABLE IV. Complications After Liver Resection of Noncolorectal Metastases (n = 32)

	No.	%
Lethal complications	3	9
Intraabdominal abscess	2	6
Liver necrosis	1	3
Nonlethal complications	5	16
Intraabdominal abscess	1	3
Portal vein injury	1	3
Bile duct injury/bile accumulation	3	9

tumors. Considering the risk of generalized disease [11], candidates for hepatic resection should be thoroughly investigated with respect to extrahepatic tumor. Attempts to verify that the liver is the sole site of metastatic disease appear to be particularly important in noncolorectal nonendocrine tumors: three of seven such patients with extrahepatic metastases at the time of liver resection died from extrahepatic recurrence. As suggested by Wolf and associates [18], it may sometimes be wise to delay hepatic resection for a few months to allow time for demonstration of disseminated disease. In the present series, however, the interval between detection and resection exceeded 3 months in only one patient in the nonendocrine group.

It is concluded that hepatic resection of noncolorectal metastases is indicated, especially for endocrine primary tumors but also for other malignancies. The results of this study indicate that extrahepatic tumor growth or more than one liver tumor should preclude liver resection in nonendocrine, noncolorectal secondaries. Criteria for resection need to be improved by further studies.

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